CLAIMS

What is claimed is

1. A method of stabilizing a biologically active agent in a biodegradable polymeric delivery system, comprising:

a) forming a polymer solution comprising a solvent and a PLGA polymer which comprises from 50 to 100% lactide or lactic acid and from 50 % to 0% glycolide or glycoliic acid, wherein said lactide or lactic acid is selected from the group consisting of the L isomer, the D isomer, or a D,L racemic mixture;

b) blending from 10% to 40% (w/w) of a pore forming agent with the PLGA polymer solution to provide a resulting solution comprising the polymer and pore forming agent;

c) dispersing the biologically active agent in the resulting polymer solution; and

d) solidifying the polymer from the resulting polymer solution to provide a biodegradable polymeric system whose microclimate homogeneously maintains a pH of greater than 4 and less than 8 throughout substantially all pores within the polymer during biodegradation for at least 4 weeks.

2. The method of claim 1 wherein from 20 to 30% of the pore-forming agent is blended with PLGA polymer solution.

3. The method of claim 1 wherein the pore forming agent is polyethylene glycol having a molecular weight of from 500 to 30, 000.

4. The method of claim 1 wherein the polyethylene glycol has a molecular weight of from 4000 to 10,000.

5. The method of claim 1 wherein the pore forming agent is a water-soluble poloxamer having a molecular weight of from 500 to 30, 000.

6. The method of claim 1 wherein the poloxamer has a molecular weight of from 4000 to 10,000.

7. The method of claim 1 further comprising the step of dispersing from 0.5 to 20 % (w/w)of a basic additive selected from the group consisting of magnesium carbonate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, zinc carbonate, zinc hydroxide, zinc phosphate, aluminum hydroxide, basic aluminum carbonate, dihyroxyaluminum sodium

carbonate, dihydroxyaluminum aminoacetate, ammonium phosphate, calcium phosphate, calcium hydroxide, magaldrate, in the polymer solution of step (a).

8. A method of stabilizing a biologically active agent in a biodegradable polymeric delivery system, comprising:

a) forming a polymer solution comprising a solvent and a PLGA polymer which comprises from 50% to 100 % lactide or lactic acid and from 50 % to 0% glycolide or glycolic acid, wherein said lactide or lactic acid is selected from the group consisting of the L isomer, the D isomer, or a D,L racemic mixture;

b) dispersing from 0.5 to 20 % (w/w) of a basic additive selected from the group consisting of magnesium carbonate, magnesium hydroxide, magnesium oxide, zinc carbonate, aluminum hydroxide, calcium phosphate in the polymer solution

c) dispersing from 0.1 to 20% (w/w) of a composition comprising the agent or the agent plus carrier in the polymer solution; and

d) solidifying the polymer from the polymer solution to provide a biodegradable polymeric system whose microclimate homogeneously maintains a pH of greater than 4 and less than 8 throughout substantially all pores within the polymer during biodegradation for at least 4 weeks.

9. The method of claim 8 wherein the polymer solution comprises 50% lactide or lactic acid and 50% glycolide or glycolic acid.

10. The method of claim 8 wherein the polymer solution comprises from 40 to 1200 mg/ml of the polymer in organic solvent.

11. The method of claim 8 wherein the basic additive is magnesium carbonate.

12. The method of claim 8 wherein the composition of step c comprises a carrier.

13. The method of claim 11 wherein the carrier is selected from the group consisting of albumin, gum arabic, gelatin, dextran, a water soluble amino acid, a monosaccharide , a disaccharide, and combinations thereof.

14. The method of claim 8 wherein from 0.5 to 3.0% (w/w) of the basic additive is dispersed in the polymer solution and wherein from 5% to 20% (w/w) of the agent or a composition comprising the agent and carrier is dispersed in the polymer solution.

15. The method of claim 8 wherein from 0.5 to 3.0% (w/w) of the basic additive is dispersed

in the polymer solution and wherein from 5 % to 30% (w/w) of a pore forming agent is dispersed in the polymer solution.

16. The method of claim 8 wherein from 0.5 to 3.0% (w/w) of the basic additive is dispersed in a polymer solution comprising from 40 to 300 mg/ml of polymer in organic solvent.

17. The method of claim 8 wherein from 3.0 to 20 % of the basic additive is dispersed in the polymer solution, wherein the polymer comprises lactide and glycolide, and wherein the polymer has an inherent viscosity of 0.7 dl/g or greater.

18. The method of claim 8 wherein from 3.0 to 20 % of the basic additive is dispersed in the polymer solution comprising from 200 mg/ml to 1200 mg/ml of polymer in organic solvent.

19. A method for stabilizing a biologically active agent encapsulated in a biodegradable polymeric delivery system, comprising

a) forming a polymer solution comprising a solvent and a biodegradable polymer which produces acids during biodegradation;

b) dispersing the agent in the polymer system;

c) dispersing a composition which promotes formation of a network of interconnected pores in the polymerized polymer; and

d) solidifying the polymer from the blended polymer solution to provide a biodegradable polymeric system whose microclimate homogeneously maintains a pH of greater than 4 and less than 8 throughout substantially all pores within the polymer during biodegradation for at least 4 weeks.

20. The method of claim 19 further comprising the step of dispersing a basic additive selected from the group consisting of magnesium carbonate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, zinc carbonate, zinc hydroxide, zinc phospate, aluminum hydroxide, basic aluminum carbonate, dihyroxyaluminum sodium carbonate, dihydroxyaluminum aminoacetate, ammonium phosphate, calcium phosphate, calcium carbonate, magaldrate, in the polymer solution of step (a).

21. The method of claim 20 wherein the basic additive is selected from the group consisting of magnesium carbonate, magnesium hydroxide, calcium carbonate, zinc hydroxide, and zinc carbonate.

21. A biodegradable polymeric delivery system for stabilizing biologically active agents encapsulated therein wherein said delivery system comprises

(a) a PLGA polymer

(b) from 0.5 to 20 % by weight of a composition which comprises the agent or a combination of the agent and a carrier; and

(c) from 0.5 % to 20% by weight of a basic additive selected from the group consisting of magnesium carbonate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, zinc carbonate, zinc hydroxide, zinc phospate, aluminum hydroxide, basic aluminum carbonate, dihyroxyaluminum sodium carbonate, dihydroxyaluminum aminoacetate, ammonium phosphate, calcium phosphate, calcium hydroxide, magaldrate, in the polymer solution of step (a); and

(d) a microclimate which maintains a pH of greater than 3 and less than 9 during biodegradation.

22. The delivery system of claim 21 wherein the PLGA polymer comprises 50% D.L lactide or lactic acid and 50% glycolide or glycolic acid.

23. The delivery system of claim 22 wherein the agent is selected from the group consisting of bone morphogenic protein-2, fibroblast growth factor, and tPA.

24. The delivery system of claim 22 wherein the delivery system is in the form of a millicylinder, wherein the agent is bone morphogenic protein-2, and wherein the basic additive is magnesium hydroxide, zinc carbonate, or magnesium carbonate.

25. The delivery system of claim 22 wherein the delivery system is in the form of a microsphere, wherein the agent is bone morphogenic protein 2, wherein the composition comprises a carrier, and wherein the basic additive is selected from the group consisting of magnesium carbonate, magnesium hydroxide, calcium hydroxide, zinc hydroxide, and zinc carbonate.